Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry Europe
European Chemical Societies Publishing

www.chemeurj.org

Hot Paper

FeIII-Based Eutectic Mixtures as Multi-task and Reusable Reaction Media for Efficient and Selective Conversion of Alkynes into Carbonyl Compounds

Marina Ramos-Martín,[a] Nicolas Ríos-Lombardía,[a, b] Javier González-Sabín,[b] Sergio E. García-Garrido,[a] Carmen Concellón,[a] Alejandro Presa Soto,*[a] Vicente del Amo,*[a] and Joaquín García-Álvarez*[a]

An efficient, simple and general protocol for the selective hydration of terminal alkynes into the corresponding methyl ketones has been developed by using a cheap, easy-to-synthesise and sustainable FeIII-based eutectic mixture [FeCl$_3\cdot$6H$_2$O/*Gly* (3:1)] as both promoter and solvent for the hydration reaction, working: i) under mild (45 °C) and bench-type reaction conditions (air); and ii) in the absence of ligands, co-catalysts, co-solvents or toxic, non-abundant and expensive noble transition metals (Au, Ru, Pd). When the final methyl ketones are solid/insoluble in the eutectic mixture, the hydration reaction takes place in 30 min, and the obtained methyl ketones can be isolated by simply decanting the liquid FeIII-*DES*, allowing the direct isolation of the desired ketones without *VOC* solvents. By using this straightforward and simple isolation protocol, we have been able to recycle the FeIII-based eutectic mixture system up to eight consecutive times. Furthermore, the FeIII-eutectic mixture is able to promote the selective and efficient formal oxidation of internal alkynes into 1,2-diketones, with the possibility of recycling this system up to three consecutive times. Preliminary investigations into a possible mechanism for the oxidation of the internal alkynes seem to indicate that it proceeds through the formation of the corresponding methyl ketones and α-chloroketones.

Introduction

Synthetic organic chemistry has greatly contributed to increasing the level of well-being, wealth and health of humanity,[1] providing our society with wide variety of organic polymeric and plastic materials, bactericidal agents, vaccines and drugs, among others.[2] However, this scientific and technological development usually required the use of sophisticated catalytic reactions which frequently rely on the use of toxic, non-abundant and expensive precious transition-metal-based compounds as catalysts.[3] In addition, a large part of the organic solvents conventionally used in traditional synthetic protocols, which are known as volatile organic compounds (*VOCs*) are usually: i) toxic; ii) flammable; and in some cases, even iii) carcinogenic.[4] Moreover, these toxic and non-renewable *VOC* solvents account for a very high percentage of the waste generated in synthetic organic protocols.[5] As a possible solution for these drawbacks, synthetic organic chemists could try to employ methodologies which did not use any solvent.[6] Although this approach present obvious advantages, the practical implementation is not always straightforward specially in the case of solid reactants. Thus, the use of solvents in organic synthesis presents several important advantages related to the so-called beneficial "solvent effect" which allows: i) easy control of the heat flow of the reaction; ii) fast and safe conversions; iii) prevention formation of unwanted side-products by dilution; and iv) stabilising transition metal catalysts.[7] Therefore, the synthetic organic community has focused its attention on finding and using neoteric benign solvents which can also promote/catalyse different organic transformation.[8] In this vein, a new class of unconventional reaction media, the deep eutectic solvents (*DESs*) have been proposed as alternative media in organic chemistry.[9] As the components of *DESs* usually come from renewable sources, these eutectic solvents are replacing toxic and volatile organic compounds (*VOCs*) in many fields such as catalysis, main-group chemistry, electrochemistry, solar technology, or in food and pharmaceutical formulations.[10]

In particular, Brønsted-type acidic *DESs* (which are formed when natural occurring carboxylic acids are used as hydrogen-bond-donors) have been applied as both solvents and

[a] M. Ramos-Martín, Dr. N. Ríos-Lombardía, Dr. S. E. García-Garrido, Dr. C. Concellón, Dr. A. Presa Soto, Dr. V. del Amo, Dr. J. García-Álvarez
Laboratorio de Química Sintética Sostenible (QuimSinSos)
Departamento de Química Orgánica e Inorgánica, (IUQOEM)
Centro de Innovación en Química Avanzada (ORFEO-CINQA)
Facultad de Química, Universidad de Oviedo
E33071 Oviedo (Spain).
E-mail: presaalejandro@uniovi.es
vdelamo@uniovi.es
garciajoaquin@uniovi.es

[b] Dr. N. Ríos-Lombardía, Dr. J. González-Sabín
Entrechem SL, Vivero Ciencias de la Salud
Colegio Santo Domingo de Guzmán
s/n 33011 Oviedo (Spain)

Chem. Eur. J. **2023**, 29, e202301736 (1 of 9)

© 2023 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry
Europe
European Chemical
Societies Publishing

promoters/catalysts for a wide variety of organic transformations.[11,12] On the other hand, their corresponding Lewis-type acidic *DESs* counterparts (which are obtained by using metallic salts as components of the eutectic mixture) have been predominantly employed in the treatment of lignocellulosic biomass,[13] being their use as promoters/catalysts in organic synthesis still in its infancy.[11,14] In this chemistry, the most commonly employed metallic salts are $ZnCl_2$ or $SnCl_2$, being their corresponding eutectic mixtures capable of promoting/catalysing different condensation reactions.[15,16] However, and as far as we are aware, Fe^III-based eutectic mixtures have been being only used to promote: i) the multicomponent conversion of an aqueous glycoaldehyde solution into 2,3-dihydrofurans (Scheme 1a);[17a] and ii) the Meyer-Schuster isomerisation of alkynols, reported by our research group (Scheme 1b).[17b,18]

In the view of scarcely studied catalytic performance of Fe^III-based *DESs* in organic synthesis and their ability to activate unsaturated organic substrates,[17b] we have decided to investigate their catalytic activity in the alkyne hydration (Scheme 1c). Hydration of alkynes is an interesting synthetic tool to produce carbonyl compounds,[19] being moreover this hydration protocol a 100% atom economy procedure.[20,21] Regarding the nature of the transition metal catalysts employed in the hydration protocol, we can mention Hg-based catalytic systems[22] and catalytic species based on metals of the platinum group (Ru, Pd, Pt, Au, and Rh).[19a–c,23] As noble metals are expensive and not abundant, it is of paramount importance to find alternatives especially among more sustainable first-row transition metals.[24–30] In this regard, few Fe-based catalytic systems for the hydration of alkynes have been reported.[27] Moreover, the vast majority of these procedures require: i) high temperatures; and ii) the presence of co-catalysts or co-solvents.[27d,31]

With all these precedents in mind, we envisioned to perform an alkyne hydration in a reactive, recyclable and sustainable Fe^III-based *DESs*, which mediated this organic transformation under typical bench (room temperature and absence of any protective atmosphere) conditions and in absence of other co-catalyst or co-solvents. Ideally, this reactive reaction media could allow the direct isolation of the final product without any purification step. Thus, we herein describe a convenient and general methodology for the selective hydration of terminal alkynes by using $FeCl_3 \cdot 6H_2O$/*Gly* (3:1) as both promoter and reaction media (Scheme 1c). Interestingly, the Fe^III-eutectic mixture also promotes the selective and efficient formal oxidation of internal alkynes into the corresponding 1,2-diketones (Scheme 1c). Importantly, this Fe^III-based eutectic mixture is able to promote this hydration/oxidation reaction: i) under standard aerobic conditions; ii) in the absence of co-catalysts or co-solvents; iii) producing selectively methyl ketones or 1,2-diketone products; and iv) could be recycled up to eight consecutive runs without using any toxic or non-renewable *VOC* solvent.

Results and Discussion

Thus, taking into account these commonly observed drawbacks in the transition-metal-mediated hydration of alkynes and inspired by our preliminary results in the use of Fe^III-based eutectic mixtures as promoters of the isomerization of propargylic alcohols,[17b] we decided to start our investigations by evaluating the activity of different acidic *DESs* (both Brønsted or Lewis-type acidic DESs were tested) in the hydration of terminal alkynes using, as a model reaction, the hydration of the commercially available phenyl acetylene (**1a**) into the corresponding acetophenone (**2a**; Table 1). To start with, we used the aforementioned eutectic mixture $FeCl_3 \cdot 6H_2O$/*Gly* [3:1 mol·mol^{-1}; see Supporting Information for characterization details (FTIR and DSC) of the employed eutectic mixture] as both solvent and promoter of the hydration reaction, working at room temperature and in the presence of air/moisture at 0.3 M concentration. However, under these reaction conditions, the eutectic mixture worked poorly and the starting alkyne **1a** was recovered (entry 1, Table 1). In the following attempt, the temperature was increased up to 45 °C, and alkyne **1a** was completely hydrated into the corresponding acetophenone (**2a**) after 24 h of reaction (entry 2, Table 1) with total chemoselectivity, as no side reactions (e.g., addition of glycerol into the C≡C triple bond or polymerisation processes) were detected by means of GC or ^{1}H NMR analyses. Finally, we should mention that the use of higher concentration of **1a** (1.0 or 1.5 M) increased the reaction time needed to achieve complete conversion into **2a**.

To gain more insight into the possible synergistic effect of the two components present in the Fe^III-based eutectic solvent in the hydration of **1a**, we decided to design two different blank experiments. In the first case, the prototypical hydration of phenyl acetylene (**1a**) was run under the same reaction conditions (45 °C, presence of air/moisture) but using the mixture *ChCl*/$FeCl_3 \cdot 6H_2O$ as solvent (1:2 mol·mol^{-1}; *ChCl* = choline chloride; entry 3, Table 2). In a second experiment, a solution of PhC≡CH (**1a**) in glycerol was treated with $FeCl_3 \cdot 6H_2O$ (10 or 40 mol% loadings were employed, entries 4 and 5 in Table 1). In all cases, GC analysis of the reaction crude
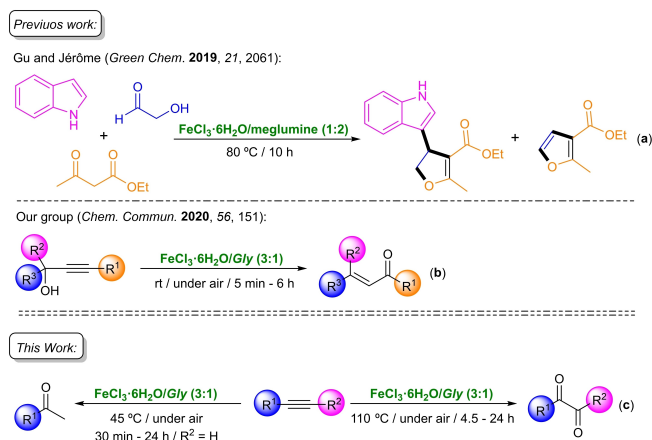
Scheme 1. Fe^III-based eutectic mixtures as non-innocent solvents (promoters) of different synthetic organic transformations.

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry Europe
European Chemical
Societies Publishing

Table 1. Hydration of phenyl acetylene (**1a**) into acetophenone (**2a**) promoted by different Lewis- or Brønsted-type deep eutectic mixtures under bench-type reaction conditions.[a]

$$Ph\text{---}\equiv \xrightarrow[\text{Temp. / under air / 24 h}]{\text{Acidic } DESs} Ph\text{-C(=O)-CH}_3$$
(**1a**) → (**2a**)

	Acidic DES[b] or solvent	Catalyst	T [°C]	Conv. [%][c]
1	FeCl$_3$·6H$_2$O/*Gly* (3:1)	–	Rt	–
2	FeCl$_3$·6H$_2$O/*Gly* (3:1)	–	45	99
3	*ChCl*/FeCl$_3$·6H$_2$O (1:2)	–	45	6
4	*Gly*	FeCl$_3$·6H$_2$O (10 mol%)	45	–
5	*Gly*	FeCl$_3$·6H$_2$O (40 mol%)	45	–
6	neat	FeCl$_3$·6H$_2$O (10 mol%)	45	34
7	toluene	FeCl$_3$·6H$_2$O (10 mol%)	45	–
8	THF	FeCl$_3$·6H$_2$O (10 mol%)	45	–
9	Et$_2$O	FeCl$_3$·6H$_2$O (10 mol%)	45	–
10	CPME	FeCl$_3$·6H$_2$O (10 mol%)	45	–
11	*ChCl*/ZnCl$_2$ (1:2)	–	45	–
12	ZnCl$_2$/*Gly* (2:1)	–	45	–
13	*ChCl*/malonic acid (1:1)	–	45	–
14	camphorsulfonic acid/*ChCl* (1:1)	–	45	–
15	*ChCl*/oxalic acid (1:1)	–	45	12
16	camphorsulfonic acid/*EG* (1:3)	–	45	3

[a] General conditions: Reactions performed under air/moisture, at the desired temperature, using 0.3 mmol of phenyl acetylene (**1a**) in 1 mL of the desired *DESs* or solvent. [b] Molar ratio of components of *DESs*. [c] Conversions determined by GC using decane as internal standard.
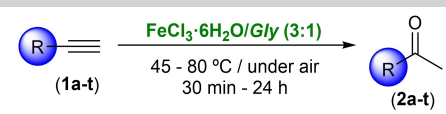
revealed the presence of unreacted starting material **1a** with only minor undefined products. Thus, these experimental results seem to indicate the critical and synergistic role played by the two components of the eutectic mixture (FeCl$_3$·6H$_2$O salt and glycerol) to ensure a successful outcome of the hydration reaction of **1a**, which cannot be replicated by the isolated components. In the same line, and as illustrated in entry 6 (Table 1), the employment of FeCl$_3$·6H$_2$O by its own under neat conditions (in the absence of any external solvent) clearly erodes the hydration process as only 34% of acetophenone (**2a**) was detected after 24 h of reaction at 45°C. At this point, it is also worth noting that the hydration reaction is shut down in both hydrocarbon-type organic medium (toluene; entry 7, Table 1) or coordinating solvents like THF (entry 8, Table 1), ethyl ether (entry 9, Table 1) or cyclopenthyl methyl ether (CPME; entry 10, Table 1).

Finally, and bearing in mind the previous success on the use of ZnCl$_2$-based eutectic mixtures as promoters of different organic condensation reactions,[15] we decided to test several Zn^{II}-based eutectic mixtures as both solvents and promoters of the hydration reaction of PhC≡CH (**1a**, entries 11 and 12, Table 1). However, and independently of the other component of the mixture (glycerol or choline chloride), no conversion into the desired acetophenone (**2a**) was observed under the previously optimized reaction conditions (45°C under air/moisture). In the same vein, the corresponding Brønsted-type acidic *DESs* counterparts were: i) totally inactive, for the case of *ChCl*/malonic acid (1:1 mol·mol^{-1}; entry 13, Table 1) and cam-

phorsulfonic acid/*ChCl* (1:1 mol·mol^{-1}; entry 14, Table 1]; or ii) poorly effective, for the case of *ChCl*/oxalic acid (1:1 mol·mol^{-1}; entry 15, Table 1) or camphorsulfonic acid/*EG* (1:3 mol·mol^{-1}; *EG* = ethylene glycol; entry 16, Table 1]; in the hydration reaction of phenyl acetylene (**1a**). Finally, the Brønsted-type acidic *DES ChCl/p-TSA* (1:1 mol·mol^{-1}; *p-TSA* = *p*-toluenesulfonic acid) gave rise to a mixture of products containing both acetophenone (**2a**) and (1-chlorovinyl)benzene.

Encouraged by these initial findings, which demonstrate the potential that the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1 mol·mol^{-1}) presents as both solvent and promoter of the hydration of terminal alkynes under mild and standard bench experimental conditions (45°C, under air and in the absence of any co-catalyst or co-solvents), we then assessed the scope of this methodology by extending our studies to a range of terminal alkynes using the previously optimized reaction conditions (see Table 2 and the Supporting Information for detailed experimental procedures and characterization details of the synthesised ketones). Excellent to good yields (97–83%) of the desired methyl ketones **2a**–**h** were observed when using FeCl$_3$·6H$_2$O/*Gly* (3:1 mol·mol^{-1}) as promoter/solvent for the hydration of terminal alkynes containing different electron-donating groups, being our system compatible with the presence of the following substituents in *para*-position: i) aliphatic [Me (**1b**; entry 2, Table 2), *tert*-butyl (**1c**; entry 3, Table 2) or *n*-pentyl (**1d**; entry 4, Table 2); ii) ethereal [OMe (**1e**; entry 5, Table 2) and OPh (**1f**; entry 6, Table 2)]; iii) aromatic [phenyl

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry
Europe
European Chemical
Societies Publishing

Table 2. Hydration of terminal alkynes **1a–t** into the corresponding methyl ketones **2a–t** promoted by FeCl$_3$·6H$_2$O/*Gly* (3:1) under bench-type reaction conditions.[a]

	R^1-C≡C–H	T [°C]	Ketone (t [h])	Yield [%][b]
1	Ph (**1a**)	45	**2a** (24)	95
2	*p*-Me–Ph (**1b**)	45	**2b** (24)	83
3	*p*-*t*Bu–Ph (**1c**)	45	**2c** (24)	89
4	*p*-CH$_3$(CH$_2$)$_4$-Ph (**1d**)	45	**2d** (24)	89
5	*p*-MeO–Ph (**1e**)	45	**2e** (24)	85
6	*p*-PhO–Ph (**1f**)	45	**2f** (0.5)	93
7	*p*-Ph–Ph (**1g**)	45	**2g** (0.5)	97
8	*p*-NH$_2$–Ph (**1h**)	45	**2h** (24)	88
9	2,4,5-(CH$_3$)$_3$–Ph (**1i**)	45	**2i** (24)	98
10	*o*-MeO–Ph (**1j**)	45	**2j** (24)	89
11	*m*-MeO–Ph (**1k**)	45	**2k** (24)	90
12	*m*-Br–Ph (**1l**)	80	**2l** (24)	76
13	1-naphthalene (**1m**)	45	**2m** (24)	89
14	6-MeO-naphthalene (**1n**)	45	**2n** (0.5)	92
15	*p*-Br–Ph (**1o**)	45	**2o** (24)	10
16	*p*-Br–Ph (**1o**)	80	**2o** (24)	88
17	*o*-F–Ph (**1p**)	80	**2p** (24)	90
18	*p*-F–Ph (**1q**)	45	**2q** (24)	95
19	*p*-CN–Ph (**1r**)	80	**2r** (48)	80
20	*p*-CO$_2$Me–Ph (**1s**)	45	**2s** (72)	28
21	1,4-diethynylbenzene (**1t**)	80	**2t** (24)	96

[a] General conditions: Reactions performed under air/moisture, at the desired temperature, using 0.3 mmol of the terminal alkyne (**1a–p**) in 1 mL of FeCl$_3$·6H$_2$O/*Gly* (3:1) *DES*. [b] Isolated yields.

(**1g**; entry 7, Table 2)]; or iv) amino groups (**1h**; entry 8, Table 2). Regarding the substitution on the aromatic ring, the presence of electron-donating substituents in: i) *ortho*-position [Me (**1i**; entry 9, Table 2)) or OMe (**1j**; entry 10, Table 2); or ii) *meta*-position [OMe (**1k**; entry 11, Table 2); Br (**1l**; entry 12, Table 2)] is also permitted, giving rise to the corresponding ketones **2k,l** with good yields (76-90%) but requiring higher temperatures (80°C) for the case of the electron withdrawing group (Br in **2l**). Similarly, the Fe^{III}-based eutectic mixture is able to promote the quantitative conversion of the more challenging terminal naphthyl-based alkynes **1m,n** into the corresponding methyl ketones **2m,n** (entries 13, 14, Table 2).
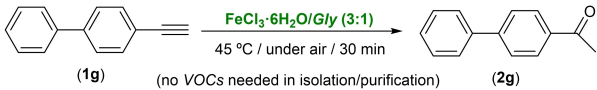
Important to note is the fact that in those cases in which the obtained methyl ketones are solid and non-soluble in the eutectic mixture (**2f**, **2g** and **2n**), we observed the formation of a precipitate after very short reaction times (30 min). Straight-forward isolation of this solid by simple decantation of the liquid FeCl$_3$·6H$_2$O/*Gly* (3:1 mol·mol^{-1}) eutectic mixture, followed by a brief washing of the organic solid with water, produces the desired methyl ketones in almost quantitative

yields (up to 97%). This easy, rapid and straightforward isolation/purification protocol opens the door to design a synthetic organic procedure in which toxic and non-biorenewable *VOC* solvents are not needed at any moment, in clear concordance with the principles of green chemistry.

Conversely, and as previously observed in earlier hydration protocols[19] and in entry 12 (Table 2), when electron-withdrawing groups are present in the aromatic ring of phenyl acetylene [Br (**1o**); entry 15, Table 2] poor yields (10%) was obtained when working at 45°C for 24 h. However, this inactivity can be simply circumvented by increasing the reaction temperature up to 80°C (entry 16, Table 2), observing again a good yield for the corresponding methyl ketone. In the same line, the presence of fluorine in *ortho*-position of the aromatic ring in the terminal alkyne **1p** requires the employment of 80°C as reaction temperature (entry 17, Table 2). However, and as previously reported by Cai and co-workers,[32] the simple translocation of the fluoride substituent into the *para* position of the aromatic ring allows decreasing the reaction temperature down to 45°C (entry 18, Table 2). Nevertheless, the presence of a nitrile or ester group in the starting alkyne (**1r,s**, entries 19–20, Table 2) requires to increase: i) both the temperature (80°C) and the reaction time (48 h) for **1r** (entry 19); or ii) the reaction time for **1s** (72 h, entry 20) to obtain only low to moderate yields of the desired methyl ketones **2r,s**. Conversely, the presence of an acrylic group in the starting alkyne (ethyl phenylpropiolate) shoots down completely the hydration protocol. Finally, it is important to mention that the Fe^{III}-based eutectic mixture is also capable of promoting the quantitative conversion of diynes (like 1,4-diethynylbenzene, **1t**) into the desired diketone **2t** (entry 21, Table 2) through a concomitant double hydration process of both C≡C bonds present in the diyne, employing the same reaction time (24 h).

The use of *DES*s as both solvents/promoters in organic synthesis opens the possibility of its recycling.[10,11,33] However, usually, a separation of the organic product through extraction with toxic and non-biorenewable organic solvents (*VOCs*) is mandatory in these methodologies.[10,11,14] Thus, the recycling of the eutectic mixture used as promoter/solvent in the organic transformation under study, without using toxic and non-renewable extracting organic solvent, it would open the door to design synthetic organic protocols in which organic and toxic *VOCs* are not needed at any stage of the synthetic protocol, not even in the purification/isolation steps. Therefore, and considering the previously observed precipitation of the final diaromatic ketone **2g** in the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1), which allows its simple isolation by decantation (no *VOCs* are needed), we decided to study the recyclability of the Fe^{III}-based eutectic mixture in the hydration of the terminal alkyne **1g** as a model substrate (see Table 3 and the Supporting Information for further experimental details). Thus, under the mild reaction conditions indicated in entry 7 of Table 2 (45°C, under air) and working with 0.3 M concentration of **1g**, we have found that the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1) could be recycled up to 8 consecutive times, finding only a minor erosion of the activity in the seventh and eight cycles (drooping from 97 to 93–90%). Finally, we should mention that the concentration of

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry Europe
European Chemical
Societies Publishing

Table 3. FeCl$_3$·6H$_2$O/*Gly* (3:1) as promoter of the hydration of terminal alkyne **1g** into the diaromatic ketone **2g** under bench type reaction conditions (45 °C and under air) and in the absence of *VOC* solvents: recycling studies.[a]
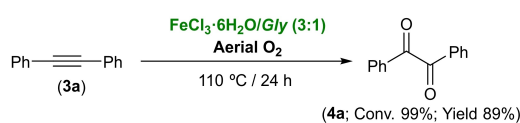

FeCl$_3$·6H$_2$O/*Gly* (3:1)
45 °C / under air / 30 min
(no *VOCs* needed in isolation/purification)

(1g) → (2g)

Cycle	Conv. [%][b]	Yield [%][c]	Cycle	Conv. [%][b]	Yield [%][c]
1	99	97	5	99	97
2	99	97	6	99	97
3	99	97	7	99	93
4	99	97	8	99	90

[a] General conditions: Reactions performed under air/moisture, at 45 °C, using alkyne **1g** (0.3 M concentration) in the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1). [b] Conversions determined by GC using decane as internal standard. [c] Isolated yields.

alkyne **1g** could be increased up to 1.5 M observing again quantitative conversion (99%) working at 45 °C and under air but needing now 1 h of reaction (we observed a similar increase in the reaction time for the hydration reaction when increasing the concentration of the alkyne in the parametrization studies for substrate **1a**). To better quantify the green credentials of the synthetic process developed, we calculated the Sheldon's environmental factor (*E*-factor; total mass of waste/mass of product),[34] finding a value of 10,[35] which is in the range of values suggested for fine chemicals (between 5 and 50).[34]

Taking into account our good results in the hydration of terminal alkynes, and trying to find the limits of our protocol, we next decided to focus our attention in the more challenging hydration of internal alkynes. This transformation usually takes place under stronger reaction conditions due to stability of the metal-π-alkyne intermediate, thus slowing the attack of water or proto-demetallation steps.[19] Moreover, formation of two different carbonyl regioisomers (Markovnikov or anti-Markovnikov), are usually observed in the hydration of internal alkynes. For the specific case of FeCl$_3$-promoted hydration of internal alkynes, the need of an external Brønsted-type co-catalyst (i.e., methansulfonic or acetic acid) has been previously reported.[27e,h] Nevertheless bearing in mind the high activity shown by the Fe^{III}-based *DESs* in the hydration of terminal alkynes, we decided to study the hydration of the symmetric diphenylacetylene (Ph–C≡C–Ph, **3a**), in the absence of any Brønsted-type acidic co-catalyst (Scheme 2; see the Supporting Information for detailed experimental procedures). After an initial parametrization study, we observed that increase of the
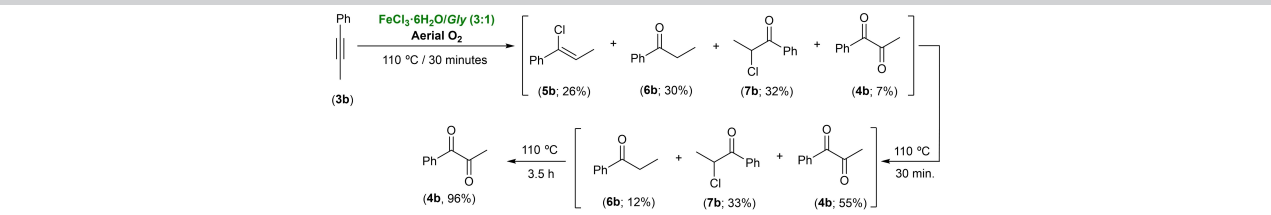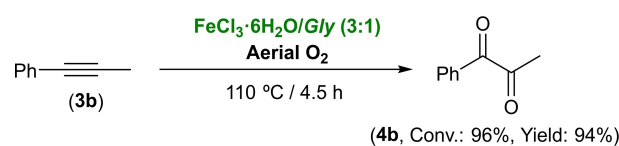
reaction temperature from 45 to 110 °C was mandatory to afford quantitative conversion of the internal alkyne **3a** after 24 h of reaction. Surprisingly, we did not observed the formation of the expected 2-phenylacetophenone [i.e., deoxybenzoin PhC(=O)CH$_2$Ph] but the corresponding 1,2-dicarbonyl compound **4a** (benzil; see supporting Information for characterization details) as a result of the formal double oxidation of the diphenylacetylene (**3a**).[36] This type of 1,2-diketones plays a major role in organic synthesis as they are valuable synthetized precursors of chiral diols,[37] *N*-heterocyclic carbenes[38] and *α*-diimine ligands.[39] Moreover, these 1,2-diketones are very important building blocks for the synthesis of biologically and medicinally relevant heterocyclic products,[40] being the proper benzils: i) natural occurring (i.e., scandione and calophione);[41] and ii) considered important drugs with antitumor, antimicrobial and cytotoxic activity.[42]

The research field related with the oxidation of internal alkynes into the corresponding 1,2-diketones has received great attention during the last decades, being this interesting transformation usually promoted by using strong oxidants,[43] photo-oxidative conditions,[44] or electrochemical transformations.[45] In the specific case of the transition-metal-based oxidations of internal alkynes, the employment of precious, toxic and expensive noble transition metals (i.e., Pd, Au, Ru) dominates the field.[46] As far as we are concerned, only a reduced number of approaches have been reported in the literature which describe the use of FeCl$_3$ in the oxidation of internal alkynes, being in most of the cases mandatory the use of strong external oxidants (H$_2$O$_2$, *t*BuOOH), different *N*-based ligands or microwave irradiation to achieve good conversions.[47] However, in our case, the Fe^{III}-based *DES* is capable of promoting the desired oxidation protocol in the absence of co-oxidants [apart from aerial O$_2$ (1 atm air)] and without the need of external ligands. Moreover, our process take place with total chemoselectivity (no side products were detected), as the previously reported and competing oxidative cleavage of the internal alkyne into the corresponding carboxylic acids was not observed.[47e] In the same line, the previously reported acetalisation of glycerol and ketones/aldehydes catalysed by FeCl$_3$·6H$_2$O as side reaction was not observed when employing our system.

Encouraged by these results, we decided to examine the behaviour of the Fe^{III}-eutectic mixture when employing non-symmetric internal alkynes, like 1-phenyl-propyne (**3b**). In this case, the use of the aforementioned reaction conditions (110 °C, under air) afforded the desired 1-phenylpropane-1,2-dione (**4b**) in 94% yield after only 4.5 h of reaction (Scheme 3; see the Supporting Information for characterization details).
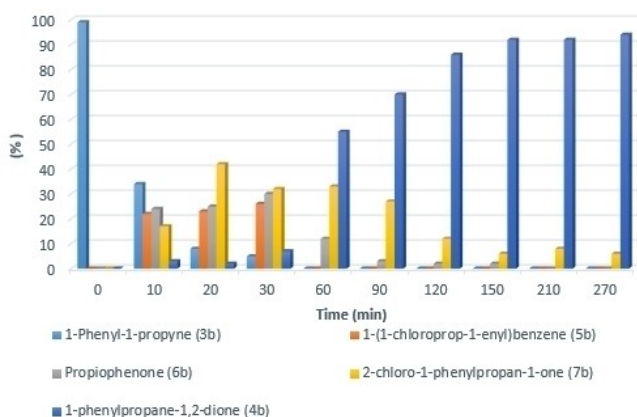

Ph ≡ Ph (3a)
FeCl$_3$·6H$_2$O/*Gly* (3:1)
Aerial O$_2$
110 °C / 24 h
→ Ph—C(=O)—C(=O)—Ph
(4a; Conv. 99%; Yield 89%)

Scheme 2. Oxidation of diphenylacetylene (**3a**) to benzil (**4a**) promoted by the acidic DES FeCl$_3$·6H$_2$O/*Gly* (3:1) under bench-type reaction conditions.

Ph ≡ (3b)
FeCl$_3$·6H$_2$O/*Gly* (3:1)
Aerial O$_2$
110 °C / 4.5 h
→ Ph—C(=O)—C(=O)—CH$_3$
(4b, Conv.: 96%, Yield: 94%)

Scheme 3. Oxidation of 1-phenylpropyne (**3b**) into 1-phenylpropane-1,2-dione (**4b**) promoted by the acidic *DES* FeCl$_3$·6H$_2$O/*Gly* (3:1) under bench-type reaction conditions.

Table 4. Preliminary investigations on a possible mechanism for the oxidation of 1-phenyl-propyne (**3b**) into 1-phenylpropane-1,2-dione (**4b**) promoted by the acidic *DES* FeCl$_3$·6H$_2$O/*Gly* (3:1) under bench type reaction conditions.[a]

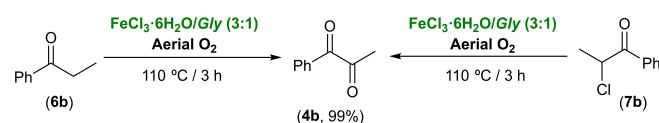|	t [min]	3b [%][b]	5b [%][b]	6b [%][b]	7b [%][b]	4b [%][b]
1	0	99	–	–	–	–
2	10	34	22	24	17	3
3	20	8	23	25	41	3
4	30	5	26	30	32	7
5	60	–	–	12	33	55
6	90	–	–	3	27	70
7	120	–	–	2	12	86
8	150	–	–	2	6	92
9	210	–	–	–	8	92
10	270	–	–	–	4	96

[a] General conditions: Reaction performed under air/moisture, at 110 °C, using 0.3 mmol of alkyne **3b** in 1 mL of the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1).
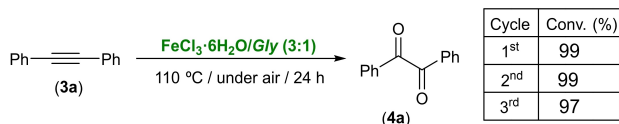[b] Ratios of products determined by GC using decane as internal standard.

Trying to shed some light on the possible mechanism involving the conversion of the internal alkyne **3b** into the corresponding 1,2-diketone **4b**, we decided to follow this reaction at different reaction times by using GC analysis (Table 4 and Figure 1). Thus, in the first 30 min of reaction, we observed almost total consumption of the starting alkyne **3b** and the formation of a reaction mixture containing 3 different products (in a ca. 1:1:1 ratio, entry 4 Table 4) apart from the desired 1,2-diketone **4b**, which is only formed in very minor amount (7%). This reaction mixture contains: i) 1-(1-chloroprop-1-enyl)benzene (**5b**), which is the expected intermediate previously postulated in FeCl$_3$-mediated hydrations of alkynes into ketones;[27e,h] ii) propiophenone (**6b**), which is the expected

ketone derived from the traditional hydration of alkyne **3b**; and iii) 2-chloro-1-phenylpropan-1-one (**7b**), which is the formal product obtained after chlorination in α-position of propiophenone. After 1 h of reaction (entry 5, Table 4), total consumption of intermediate **5b** was observed, thus containing now the reaction mixture: i) propiophenone (**6b**; 12%); ii) the alpha-chlorinated propiophenone **7b** (33%); and iii) the desired 1,2-diketone **4b** (55%). Subsequent 3.5 h of reaction are needed to convert in turns, propiophenone **6b** into the chlorinated product **7b**, and final conversion of **7b** into the 1,2-diketone **4b** (see entries 6–10 in Table 4). Here, it is important to mention that in independent blank experiments (Scheme 4), we have been able to prove that the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1) is capable of promoting the conversion of pure propiophenone **6b** or its chlorinated derivate **7b** into the 1,2-diketone **4b**, being thus in good agreement with the proposed mechanism shown in Table 4.[48]

Finally, we decided to investigate the level of reusability of the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1) in the conversion of the internal alkyne **3a** into the corresponding benzil (**4a**, Scheme 5; see the Supporting Information for further experimental details). Thus, we found that the eutectic mixture FeCl$_3$·6H$_2$O/*Gly* (3:1) could be recycled up to three consecutive

Figure 1. Study of the product distribution as function of time in the FeCl$_3$·6H$_2$O/Gly (3:1) mediated hydration of the internal alkyne **3b** into 1,2-diketone **4b** working at 110 °C and under bench type reaction conditions.

Scheme 4. Blank experiments as proof of conversion of reaction intermediates **6b** and **7b** into the corresponding 1,2-diketone **4b**.

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry Europe
European Chemical
Societies Publishing

Scheme 5. FeCl₃·6H₂O/*Gly* (3:1) as promoter of the oxidation of internal alkyne **3a** into benzil (**4a**) under bench type reaction conditions (110 °C and under air): recycling studies.

runs, although in this case it is mandatory the use of a liquid-liquid extraction procedure to separate the final organic product from the eutectic mixture, as no precipitation of benzil (**4a**) was observed. In this field, the selection of the extracting organic solvent is a key point as it should fulfil the following principles: i) be immiscible with *DES*; ii) be effective in the extraction of the organic products; and iii) present a favourable sustainable footprint. Taking into account all these points, the biomass derived solvent cyrene was selected as an ideal extracting solvent in our recycling protocol as it accomplishes all the aforementioned principles.[49] For the first three cycles, we observed quantitative conversions of the internal alkyne **3a** into benzil (**4a**) after 24 h of reaction at 110 °C and under air. However, after the third recycling, erosion of the eutectic mixture was observed, being now unable to promote the desired reaction in any additional cycle.

Conclusions

In summary, this work introduces the eutectic mixture FeCl₃·6H₂O/*Gly* (3:1) as a superior promoter/reaction medium for the selective and efficient hydration of terminal alkynes into the corresponding methyl ketones. The reaction proceeds under remarkably mild (45 °C) and bench-type conditions (under moisture/air), displaying a broad substrate scope. Moreover, the following features of our hydration system merit highlighting: i) it takes place in the absence of external ligands; ii) co-catalysts (Brønsted acids) or co-solvents (MeOH) are not required; and iii) when final ketones are solid and insoluble in the eutectic mixture, isolation by simple decantation is possible (no *VOC* solvents are needed). Moreover, as the hydration reaction can be efficiently recycled (up to 8 consecutive cycles) without using *VOC* solvents, the practical application of our methodology provides a complementary synthetic tool to the traditional hydration of terminal alkynes, which usually requires the use of toxic, non-abundant and expensive noble transition metals (like Au, Ru or Pd).

Finally, the Fe^{III}-eutectic mixture can be considered as a multi-task reaction kit as it is also able to promote the efficient and selective formal oxidation of internal alkynes into the corresponding 1,2-diketones, just by using aerial O₂ as co-oxidant (strong oxidants like H₂O₂ or *t*BuOOH are not needed). Again this oxidation protocol can be efficiently recycled up to three consecutive times. Moreover, a preliminary study on a possible mechanism for the oxidation of internal alkynes into 1,2-ketones is presented.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

[1] K. C. Nicolau, *Proc. R. Soc. A* **2014**, *470*, 20130690.
[2] a) *Organic Materials for Sustainable Construction* (Ed.: Y. Mouton), Wiley, Hoboken, **2013**; b) C. F. Nising, F. von Nussbaum, *Eur. J. Org. Chem.* **2022**, e202200252.
[3] A recent editorial in *Organic Process Research and Development* highlights the actual efforts devoted to the synthesis of fine chemicals and pharmaceuticals using non-precious metals: a) J. R. Dunetz, D. Fandrick, H.-J. Federsel, *Org. Process Res. Dev.* **2015**, *19*, 1325. For a recent review in this field, see: b) F. Buono, T. Nguyen, B. Qu, H. Wu, N. Haddad, *Org. Process Res. Dev.* **2021**, *25*, 1471.
[4] a) R. Heinrich-Ramm, M. Jakubowski, B. Heinzow, J. M. Christensen, E. Olsen, O. Hertel, *Pure Appl. Chem.* **2000**, *72*, 385; b) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2009**, *39*, 301.
[5] D. J. C. Constable, C. Jimenez-Gonzalez, R. K. Henderson, *Org. Process Res. Dev.* **2007**, *11*, 133.
[6] J. A. Gladysz, *Chem* **2018**, *4*, 2007.
[7] C. Reichardt, *Solvents and Solvent Effects* in Organic Chemistry, Wiley-VCH, Weinheim, **2004**.
[8] For example, traditional ionic liquids (ILs), dimethyl carbonate or water have been used as unconventional solvents playing a dual role as the reaction medium and reagent/promoter/catalyst in organic synthesis: a) S. Chowdhury, R. S. Mohan, J. L. Scott, *Tetrahedron* **2007**, *63*, 2363; b) R. Porcar, P. Lozano, M. I. Burguete, E. Garcia-Verdugo, S. V. Luis, *React. Chem. Eng.* **2018**, *3*, 572; c) M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou, B. H. Lipshutz, *Chem. Sci.* **2021**, *12*, 4237.
[9] Deep eutectic solvents (*DESs*) are binary or ternary mixtures comprising at least one hydrogen bond acceptor (*HBA*) and at least one hydrogen bond donor (*HBD*) with a melting point much lower than that of either of the individual components and that of an ideal liquid mixture. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed, V. Tambyrajah, *Chem. Commun.* **2003**, 70.
[10] a) J. García-Álvarez, *Deep Eutectic Solvents and Their Applications as New Green and Biorenewable Reaction Media, in Handbook of Solvents, Vol. 2: Use, Health, and Environment*, 3rd ed. (Ed.: G. Wypych), ChemTec Publishing, Toronto, **2019**; b) B. B. Hansen, S. Spittle, B. Chen, D. Poe, Y. Zhang, J. M. Klein, A. Horton, L. Adhikari, T. Zelovich, B. W. Doherty, B. Gurkan, E. J. Maginn, A. Ragauskas, M. Dadmun, T. A. Zawodzinski, G. A. Baker, M. E. Tuckerman, R. F. Savinell, J. R. Sangoro, *Chem. Rev.* **2021**, *121*, 1232.
[11] For recent revisions in this field see: a) A. E. Ünlu, A. Arikaya, S. Takaç, *Green Process Synth.* **2019**, *8*, 355; b) S. E. Hooshmand, S. Kumarl, I. Bahadur, T. Singh, R. S. Varma, *J. Mol. Liq.* **2023**, *371*, 121013.
[12] a) V. De Santi, F. Cardellini, L. Brinchi, R. Germani, *Tetrahedron Lett.* **2012**, *53*, 5151; b) A. Hayyan, M. Ali Hashim, F. S. Mjalli, M. Hayyan, I. M.

Chem. Eur. J. **2023**, *29*, e202301736 (7 of 9)

© 2023 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry
Europe
European Chemical
Societies Publishing

AlNashef, *Chem. Eng. Sci.* **2013**, *92*, 81; c) M. Tiecco, R. Germani, F. Cardellini, *RSC Adv.* **2016**, *6*, 43740; d) X. Jin, A. Wang, H. Cao, S. Zhang, L. Wang, X. Zheng, X. Zheng, *Res. Chem. Intermed.* **2018**, *44*, 5521; e) S. Nejrotti, M. Iannicelli, S. S. Jamil, D. Arnodo, M. Blangetti, C. Prandi, *Green Chem.* **2020**, *22*, 110; f) D. Arnodo, C. Meazzo, S. Baldino, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2023**, *29*, e202300820; g) D. Arnodo, E. De Nardo, S. Ghinato, S. Baldino, M. Blangetti, C. Prandi, *ChemSusChem* **2023**, *16*, e202202066.

[13] For recent and selected works in this field, see: a) H. Lian, S. Hong, A. Carranza, J. D. Mota-Morales, J. A. Pojman, *RSC Adv.* **2015**, *5*, 28778; b) F. Liu, Z. Xue, X. Zhao, H. Mou, J. He, T. Mu, *Chem. Commun.* **2018**, *54*, 6140; c) Z.-K. Wang, S. Hong, J.-l. Wen, C.-Y. Ma, L. Tang, H. Jiang, J.-J. Chen, S. Li, X.-J. Shen, T.-Q. Yuan, *ACS Sustainable Chem. Eng.* **2020**, *8*, 1050; d) H. Ren, R. Gong, M. Li, Y. Liu, H. Zhu, C. Wang, E. Duan, *J. Mol. Liq.* **2020**, *312*, 113282; e) Z.-m. Li, J.-x. Long, Y.-h. Wu, M.-l. Cao, S.-j. Liu, X.-h. Li, *Ind. Eng. Chem. Res.* **2020**, *59*, 17328; f) Y. Zhu, B. Qi, X. Liang, J. Luo, Y. Wan, *Polymer* **2021**, *13*, 1170; g) F. Shen, S. Wu, M. Huang, L. Zhao, J. He, Y. Zhang, S. Deng, J. Hu, D. Tian, F. Shen, *Green Chem.* **2022**, *24*, 5242; h) C. B. T. L. Lee, T. Y. Wu, K. J. Yong, C. K. Cheng, L. F. Siow, J. Md. Jahim, *Sci. Total Environ.* **2022**, *827*, 154049.

[14] H. Qin, X. Hu, J. Wang, H. Cheng, L. Chen, Z. Qi, *Green Energy & Environ.* **2020**, *5*, 8.

[15] For examples which reported the use of ZnCl₂-based acidic *DESs* as catalysts/promoters of organic synthesis protocols, see: a) A. Zhu, L. Li, J. Wangm, K. Zhuo, *Green Chem.* **2011**, *13*, 1244; b) W. Cheng, Z. Fu, J. Wang, J. Sun, S. Zhang, *Synth. Commun.* **2012**, *42*, 2564; c) A. Wang, P. Xing, X. Zheng, H. Cao, G. Yang, X. Zheng, *RSC Adv.* **2015**, *5*, 59022; d) P. H. Tran, H. T. Nguyen, P. E. Hansen, T. N. Le, *RSC Adv.* **2016**, *6*, 37031; e) H. T. Nguyen, P. H. Tran, *RSC Adv.* **2016**, *6*, 98365.

[16] For examples which reported the use of SnCl₂-based acidic *DESs* as catalysts/promoters of organic synthesis protocols, see: a) N. Azizi, Z. Manocheri, *Res. Chem. Intermed.* **2012**, *38*, 1495; b) N. Azizi, E. Batebi, *Catal. Sci. Technol.* **2012**, *2*, 2445; c) U. B. Patil, A. S. Singh, J. M. Nagarkar, *RSC Adv.* **2014**, *4*, 1102; d) D. Shahabi, H. Tavakol, *J. Mol. Liq.* **2016**, *220*, 324.

[17] a) J. Xu, W. Huang, R. Bai, Y. Queneau, F. Jerome, Y. Gu, *Green Chem.* **2019**, *21*, 2061; b) N. Ríos-Lombardía, L. Cicco, K. Yamamoto, J. A. Hernández-Fernández, F. Morís, V. Capriati, J. García-Álvarez, J. González-Sabín, *Chem. Commun.* **2020**, *56*, 15165.

[18] Fe-based eutectic mixtures have been also recently used in: i) treatment of cellulose or lignin (see ref. [13]); ii) preparation of a FeS@graphene anodic material; iii) absorption of NH₃; iv) Fenton-like oxidation of cellulose to produce biobutanol; v) facile and efficient preparation of nitrogen-doped magnetic biochar; vi) synthesis of pillar[n]arenes; and vii) oxidative polymerization of 3-octylthiophene; a) Z. Ke, M. Mei, J. Liu, P. Du, B. Zhang, T. Wang, S. Chen, J. Li, *J. Cleaner Prod.* **2022**, *357*, 132012; b) N.-N. Cheng, Z. L. Li, H.-C. Lan, W.-L. Xu, K. Huang, *AIChE J.* **2022**, *68*, e17660; c) L. Gong, X. Wu, Y. Wang, J. Zhu, S. Wang, Y. Xiu, J. Dong, G. Xu, Y. Ni, *Biomass Convers. Biorefin.* **2022**, DOI: 10.1007/s13399-022-02940-0; d) D. Ju, X. Cao, H. Li, J. Zheng, C. Chen, Z. Wang, J. Qiu, Y. Zhang, M. Liu, Q. Zhu, *Ceram. Int.* **2022**, *48*, 13508; e) J. Cao, Y. Shang, B. Qi, X. Sun, L. Zhang, H. Liu, H. Zhang, X. Zhou, *RSC Adv.* **2015**, *5*, 9993; f) T. J. Park, S. H. Lee, *Green Chem.* **2017**, *19*, 910.

[19] a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; b) L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121; c) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43*, 3368; d) W. E. Brenzovich, *Angew. Chem. Int. Ed.* **2012**, *51*, 8933; e) R. Salvio, M. Bassetti, *Inorg. Chim. Acta* **2021**, *522*, 120288.

[20] The design of synthetic organic protocols which occur with total atom economy is highly desirable from a *Green Chemistry* point of view: a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; c) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72*, 1233; d) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695; e) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

[21] In this hydration transformation, the use of transition-metal-based species as catalysts/promoters helps to lower the otherwise unattainable energy of activation of this protocol. I. Alabugin, E. González-Rodríguez, R. Kawade, A. Stepanov, S. Vasilevsky, *Molecules* **2019**, *24*, 103.

[22] I. P. Beletskaya, *Chem. Eur. J.* **2019**, *25*, 7408.

[23] The employment of transition metal catalyst in the hydration of alkynes has been described in comprehensive reviews and accounts covering the nature of the active metal catalysts, reaction mechanisms and application in organic synthesis: a) A. Leyva-Perez, A. Corma, *Angew. Chem. Int. Ed.* **2012**, *51*, 614; b) L. Yang, C. Xu, *Chin. J. Org. Chem.* **2017**,

37, 3130; c) R. A. Widenhoefer, F. Song, *Gold-Catalyzed Addition of Oxygen Nucleophiles to C–C Multiple Bonds"*, in Catalyzed Carbon-Heteroatom Bond Formation (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2010**, pp 463–492; d) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028; e) D. Zuccaccia, A. Del Zotto, W. Baratta, *Coord. Chem. Rev.* **2019**, *396*, 103; f) C. H. Leung, M. Baron, A. Biffis, *Catalysts* **2020**, *10*, 1210; g) K. S. Egorova, V. P. Ananikov, *Angew. Chem. Int. Ed.* **2016**, *55*, 12150; h) C. Bruneau, *Group 8 Metal-Catalyzed O–H Bond Addition to Unsaturated Molecules*, in Topics in Organometallic Chemistry, Vol. 43 (Eds.: V. P. Ananikov, M. Tanaka), Springer, Berlin Heidelberg, **2013**, p. 203; i) G. Abbiati, E. M. Beccalli, E. Rossi, *Group 9 and 10 Metal-Catalyzed O–H Bond Addition to Unsaturated Molecules*, in Topics in Organometallic Chemistry, Vol. 43. (Eds.: V. P. Ananikov, M. Tanaka), Springer, Berlin Heidelberg, **2013**, p. 23.

[24] Transition metal hydration catalysts based on fourth period elements are unknown for Sc, Ti, V, Cr, Mn (see Ref. [25]) and Ni (see Ref. [26]). A synthetic procedure for the indirect anti-Markovnikov hydration of internal alkynes promoted by TiCl₄ was reported by Ackermann and Kaspar: L. Ackermann, L. T. Kaspar, *J. Org. Chem.* **2007**, *72*, 6149.

[25] It should be mentioned that manganese dioxide is an active catalyst for the hydration of nitriles. See for example: a) K. Yamaguchi, Y. Wang, H. Kobayashi, N. Mizuno, *Chem. Lett.* **2012**, *41*, 574; b) C. Battilocchio, J. M. Hawkins, S. V. Ley, *Org. Lett.* **2014**, *16*, 1060; c) C. Battilocchio, S.-H. Lau, J. M. Hawkins, S. V. Ley, *Org. Synth.* **2017**, *94*, 34.

[26] It should be noted, however, that Ni-based complexes catalysed the hydration of benzo- and acetonitrile: M. G. Crestani, A. Arévalo, J. J. García, *Adv. Synth. Catal.* **2006**, *348*, 732.

[27] a) J. P. Damiano, M. Postel, *J. Organomet. Chem.* **1996**, *522*, 303; b) P. O. Miranda, D. D. Díaz, J. l. Padrón, M. A. Ramírez, V. S. Martín, *J. Org. Chem.* **2005**, *70*, 57; c) X.-F. Wu, D. Bezier, C. Darcel, *Adv. Synth. Catal.* **2009**, *351*, 367; d) J. R. Cabrero-Antonino, A. Leyva-Pérez, A. Corma, *Chem. Eur. J.* **2012**, *18*, 11107; e) J. Park, J. Yeon, P. H. Lee, K. Lee, *Tetrahedron Lett.* **2013**, *54*, 4414; f) M. Bassetti, S. Ciceri, F. Lancia, C. Pasquini, *Tetrahedron Lett.* **2014**, *55*, 1608; g) G. Zao, G. Xu, C. Qian, W. Tang, *J. Am. Chem. Soc.* **2017**, *139*, 3360; h) A. Antenucci, P. Flamini, M. V. Fornaiolo, S. Di Silvio, S. Mazzetti, P. Mencarelli, R. Salvio, M. Bassetti, *Adv. Synth. Catal.* **2019**, *361*, 4517; i) L. R. Jefferies, S. P. Cook, *Tetrahedron* **2014**, *70*, 4204.

[28] For selected examples of Co-catalysed hydration of alkynes, see a) T. Tachinami, T. Nishimura, R. Ushimaru, R. Noyori, H. Naka, *J. Am. Chem. Soc.* **2013**, *135*, 50; b) Z. Lin, Z.-M. Zhang, Y.-S. Chen, W. Lin, *Angew. Chem. Int. Ed.* **2016**, *55*, 13739; c) S. Wang, C. Miao, W. Wang, Z. Lei, W. Sun, *Chin. J. Catal.* **2014**, *35*, 1695; d) S. Hou, H. Yang, B. Cheng, H. Zhai, Y. Li, *Chem. Commun.* **2017**, *53*, 6926; e) J.-W. Lai, Z.-Y. Liu, X.-Y. Chen, H. Zhang, H.-Y. Liu, *Tetrahedron Lett.* **2020**, *61*, 152426.

[29] Since the first reported alkyne hydration mediated by copper salts (a) S. A. Vartanyan, S. K. Pirenyan, N. G. Manasyan, *Zh. Obshch. Khim.* **1961**, *31*, 2436; b) G. K. Shestakov, N. Y. Vsesvyatskaya, A. M. Stepanov, O. N. Temkin, *Kinet. Catal.* **1976**, *17*, 815), the chemistry of Cu-based catalyst in this transformation has been extensively reviewed. See for example references 19a–c.

[30] Active Zn compounds were firstly described by Kucherov in 1909 (a) M. G. Kutscheroff, *Chem. Ber.* **1909**, *42*, 2759). However, the chemistry of zinc has been scarcely developed notwithstanding the role of the heavier elements in the group. For a selected examples of Zn-mediated alkyne hydration see: b) X. Chew, Y. Linb, Y. H. Lim, *RSC Adv.* **2014**, *4*, 16765; c) Q. Wang, M. Zhu, H. Zhang, C. Xu, B. Dai, J. Zhang, *Chem. Select* **2018**, *3*, 9603; d) Q. Wang, M. Zhu, H. Zhang, C. Xu, B. Dai, J. Zhang, *Catal. Commun.* **2019**, *120*, 33; e) Q. Wang, M. Zhu, B. Dai, J. Zhang, *Catal. Sci. Technol.* **2019**, *9*, 981.

[31] a) D. B. Grotjahn, D. A. Lev, *J. Am. Chem. Soc.* **2004**, *126*, 12232; b) N. Marion, R. S. Ramon, S. P. Nolan, *J. Am. Chem. Soc.* **2009**, *131*, 448; c) K.-i. Fujita, M. Kujime, T. Muraki, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 261; d) X. Li, G. Hu, P. Luo, G. Tang, Y. Gao, P. Xu, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2427; e) S. Liang, G. B. Hammond, B. Xu, *Chem. Commun.* **2015**, *51*, 903; f) R. E. Ebule, D. Malhotra, G. B. Hammond, B. Xu, *Adv. Synth. Catal.* **2016**, *358*, 1478; g) L. Shen, X. Han, B. Dong, Y. Yang, J. Yang, F. Li, *ACS Appl. Polym. Mater.* **2022**, *4*, 7408.

[32] H. Liu, Y. Wei, C. Cai, *Synlett* **2016**, *27*, 2378.

[33] The life cycle and the level of recyclability of these eutectic mixtures are very important factors to bear in mind. a) *Catalyst Separation, Recovery and Recycling. Chemistry and Process Design* (Eds.: D. Cole-Hamilton, R. Tooze), Springer, Dordrecht, **2006**; b) *Recoverable and Recyclable Catalyst* (Ed.: M. Benaglia), Wiley, Chichester, **2009**.

[34] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273.

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202301736

Chemistry Europe
European Chemical
Societies Publishing

[35] For more details on the *E*-factor calculation, see the Supporting Information.

[36] Some of us have previously reported the moderate activity of the FeCl$_3$·6H$_2$O/*Gly* (3:1) eutectic mixture in the oxidation of benzyl alcohol into the corresponding benzaldehyde (20% yield) when working at room temperature. L. Cicco, M. Roggio, M. López-Aguilar, R. Ramos-Martín, F. M. Perna, J. García-Álvarez, P. Vitale, V. Capriati, *ChemistryOpen* **2022**, *11*, e202200160.

[37] a) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 14960; b) L. De Luca, A. Mezzetti, *Angew. Chem. Int. Ed.* **2017**, *56*, 11949.

[38] a) A. P. Dove, H. Li, R. C. Pratt, B. G. G. Lohmeijer, D. A. Culkin, R. M. Waymouth, J. L. Hedrick, *Chem. Commun.* **2006**, 2881; b) F. Ullah, M. K. Kindermann, P. G. Jones, J. Heinicke, *Organometallics* **2009**, *28*, 2441.

[39] L. Guo, H. Gao, Q. Guan, H. Hu, J. Deng, J. Liu, F. Liu, Q. Wu, *Organometallics* **2012**, *31*, 6054.

[40] For representative examples, see: a) S. V. More, M. N. V. Sastry, C.-C. Wang, C.-F. Yao, *Tetrahedron Lett.* **2005**, *46*, 6345; b) V. Zuliani, G. Cocconcelli, M. Fantini, C. Ghiron, M. Rivara, *J. Org. Chem.* **2007**, *72*, 4551; c) G. Bratulescu, *Synthesis* **2009**, 2319; d) J.-A. Jiang, C.-Y. Du, C.-H. Gu, Y.-F. Ji, *Synlett* **2012**, *23*, 2965; e) S. Khaksar, F. Rostamnezhad, *Bull. Korean Chem. Soc.* **2012**, *33*, 2581.

[41] R. Worayuthakarn, S. Boonya-udtayan, N. Ruchirawat, N. Thasana, *Eur. J. Org. Chem.* **2014**, 2496.

[42] a) W. Li, Y. Asada, T. Yoshikawa, *Planta Med.* **1998**, *64*, 746; b) J. L. Hyatt, V. Stacy, R. M. Wadkins, K. J. P. Yoon, M. Wierdl, C. C. Edwards, M. Zeller, A. D. Hunter, M. K. Danks, G. Crundwell, P. M. Potter, *J. Med. Chem.* **2005**, *48*, 5543; c) L. D. Hicks, J. L. Hyatt, T. Moak, C. C. Edwards, L. Tsurkan, M. Wierdl, A. M. Ferreira, R. M. Wadkins, P. M. Potter, *Bioorg. Med. Chem.* **2007**, *15*, 3801; d) C. Mousset, A. Giraud, O. Provot, A. Hamze, J. Bignon, J.-M. Liu, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3266; e) S. Ganapaty, G. V. K. Srilakshmi, S. T. Pannakal, H. Rahman, H. Laatsch, R. Brun, *Phytochemistry* **2009**, *70*, 95.

[43] For selected examples, see: a) V. O. Rogatchov, V. D. Filimonov, M. S. Yusubov, *Synthesis* **2001**, 1001; b) J. H. Chu, Y.-J. Chen, M.-J. Wu, *Synthesis* **2009**, 2155; c) S.-T. Yuan, Y.-H. Wang, J.-B. Liu, G. Qiu, *Adv. Synth. Catal.* **2017**, *359*, 1981; d) S. W. Kim, T.-W. Um, S. Shin, *J. Org. Chem.* **2018**, *83*, 4703; e) S. Naidoo, V. Jeena, *Eur. J. Org. Chem.* **2019**, 1107; f) E. Cho, A. Jayaraman, J. Lee, K. C. Ko, S. Lee, *Adv. Synth. Catal.* **2019**, *361*, 1846; g) R. Gujjarappa, N. Vodnala, V. P. R. K. Putta, V. G. Reddy, C. C. Malakar, *Tetrahedron Lett.* **2020**, *61*, 151588.

[44] For recent examples, see: a) T. Hering, T. Slanina, A. Hancock, U. Wille, B. König, *Chem. Commun.* **2015**, *51*, 6568; b) X. Liu, T. Cong, P. Liu, P. Sun, *J. Org. Chem.* **2016**, *81*, 7256; c) X. Zhu, P. Li, Q. Shi, L. Wang, *Green Chem.* **2016**, *18*, 6373; d) V. Štrukil, I. Sajko, *Chem. Commun.* **2017**, *53*, 9101; e) H.-T. Qin, X. Xu, F. Liu, *ChemCatChem* **2017**, *9*, 1409.

[45] J. Zhou, X.-Z. Tao, J.-J. Dai, C.-G. Li, J. Xu, X.-M. Xu, X.-J. Xu, *Chem. Commun.* **2019**, *55*, 9208.

[46] a) W. Ren, J. Liu, L. Chen, X. Wan, *Adv. Synth. Catal.* **2010**, *352*, 1424; b) M. E. Jung, G. Deng, *Org. Lett.* **2014**, *16*, 2142; c) S. Ruengsangtongkul, N. Chaisan, C. Thongsornkleeb, J. Tummatorn, S. Ruchirawat, *Org. Lett.* **2019**, *21*, 2514; d) Y. Zhai, Z. Su, H. Jiang, J. Rong, X. Qiu, C. Tao, *Tetrahedron Lett.* **2019**, *60*, 843; e) A. Y. Dubovtsev, D. V. Darín, M. Krasavin, V. Y. Kukushkin, *Eur. J. Org. Chem.* **2019**, 1856.

[47] a) C. Sheu, A. Sobkowiak, S. Jeon, D. T. Sawyer, *J. Am. Chem. Soc.* **1990**, *112*, 879; b) C. Sheu, S. A. Richert, P. Cofré, B. Ross, Jr., A. Sobkowiak, D. T. Sawyer, J. R. Kanofsky, *J. Am. Chem. Soc.* **1990**, *112*, 1936; c) J. Y. Ryu, S. Heo, P. Park, W. Nam, J. Kim, *Inorg. Chem. Commun.* **2004**, *7*, 534; d) A. Giraud, O. Provot, J.-F. Peyrat, M. Alami, J. D. Brion, *Tetrahedron* **2006**, *62*, 7667; e) S. Enthaler, *ChemCatChem* **2011**, *3*, 1929; f) C. F. Xu, M. Xu, Y. X. Jia, C. Y. Li, *Org. Lett.* **2011**, *13*, 1556; g) S. Shi, T. Wang, M. Rudolph, A. S. K. Hasmhi, *Chem. Eur. J.* **2013**, *19*, 6576; h) S. Zaher, L. Christ, M. A. El Rahima, A. Kanj, I. Karaméa, *J. Mol. Catal.* **2017**, *438*, 204.

[48] For a graphical hypothesis of a plausible mechanism for the FeCl$_3$·6H$_2$O/*Gly* (3:1) mediated hydration/oxidation of the internal alkyne **3b** into the corresponding 1,2-diketone **4b** see Supporting Information.

[49] Dihydrolevoglucosenone (cyrene) is a bicyclic, chiral, seven-membered heterocyclic cycloalkanone. It is a bio-based and fully biodegradable dipolar aprotic solvent which is obtained from plantation radiata pine. It has been reported its use as a sustainable solvent for the production of drugs and other fine chemicals in pharmaceutical industries. "Cyrene as a Green Solvent in the Pharmaceutical Industry", I. C. Adaka, P. F. Uzor in *Green Sustainable Process for Chemical and Environmental Engineering and Science* (Eds.: R. Inamuddin, M. I. Boddula, Ahamed, A. M. Asiri), Elsevier, Amsterdam, **2021**.